BIOACTIVE AND BIODEGRADABLE COMPOSITES OF POLYMERS AND CERAMICS OR GLASSES AND METHOD TO MANUFACTURE SUCH COMPOSITES

Field of the Invention

The present invention relates to a surgical osteosynthesis composite material, which is biodegradable and bioactive, and methods of manufacturing the composite material.

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Background of the Invention

In surgery, either biostable or biodegradable devices are used for the fixation of bone fractures to immobilize the bone fragments and accelerate patient mobilization.

10 Most biostable devices are typically made of metallic alloys. *See* R.M. Pilliar, Powder Metal-Made Orthopaedic Implants With Porous Surface For Fixation By Tissue Ingrowth, Clinical Orthopaedics and Related Research, Vol. 176, 1983, pp. 42-51. Nevertheless, there are several disadvantages in the use of metallic implants. One such disadvantage is bone resorption caused by bone plates and screws, which

15 carry most of the external loads, leading to stress protection produced by the

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modulus mismatch between metals and bone. Another disadvantage is the carcinogenic potential and the possibility of corrosion. Therefore, surgeons are recommended to remove metallic bone plates and screws in a second operation once the fracture has healed.

5   Bioresorbable polymeric fracture fixation devices have been studied as replacements for metallic implants. *See* S. Vainiopää, P. Rokkanen, P. Törmälä, Surgical Applications Of Biodegradable Polymers In Human Tissue, Progress in Polymer Science, Vol. 14, 1989, pp. 679-716. The advantages of these devices are that materials resorb in the body and degradation products disappear via metabolic routes. Hence, a second operation is not required. Additionally, the strength and the stiffness of the bioresorbable polymeric devices decreases when the device degrades and hence the bone is progressively loaded (which promotes bone regeneration). One disadvantage is the relatively low strength of existing polymeric devices. In the case of cortical, bone fracture, for example, unreinforced poly lactic acid (PLLA) plate and screws are too weak initially to permit patient mobilization. *See* J. Eitenmüller, K.L. Geriach,T. Schmickal, H. Krause, An In Vivo Evaluation Of A New High Molecular Weight Polylactide Osteosynthesis Device, European Congress on Biomaterials, Bologna Italy, September 14-17, 1986, p. 94. In addition, the relatively low values of Young's modulus compared to metallic plates mean that thicker sections are required to ensure adequate stability.

Törmälä et al. have developed self-reinforced bioresorbable polymeric composites to improve the strength of bioresorbable polymer devices. These show good mechanical properties: e.g. bending strengths of 360±70 MPa and bending moduli of 12±2 GPa, respectively, have been reported. *See* P. Törmälä,

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Biodegradable Self-Reinforced Composite Materials; Manufacturing, Structure and

Mechanical Properties, Clinical Materials, Vol. 10, 1992, pp. 29-34.

A common property of most polymeric implants is the lack of bony ongrowth

to the material. In contrast, such bone apposition is produced by bioactive ceramics

5   and glasses. *See* O.H. Andersson, K.H. Karlsson, Bioactive Glass, Biomaterials

Today And Tomorrow, Proceedings of the Finnish Dental Society Days of Research,

Tampere, Finland, 10-11 November 1995, Gillot Oy, Turku, 1996, pp. 15-16. By

adding bioactive ceramics or glasses to polymers to produce a composite, the

bioactivity of the material can be improved. This effect has been demonstrated in

10   dental composites and bone cement. *See* J.C. Behiri, M. Braden, S.N. Khorashani,

D. Wiwattanadate, W. Bonfield, Advanced Bone Cement For Long Term

Orthopaedic Applications, Bioceramics, Vol. 4, ed. W. Bonfield, G.W. Hastings and

K.E. Tanner, Butterworth-Heinemann ltd, Oxford, 1991, pp. 301-307.

Bonfield et al have developed a biostable composite consisting of a

15   polyethylene matrix and a particulate hydroxyapatite reinforcement (HAPEX™). *See*

W. Bonfield, J.A. Bowman, M.D. Grynpas, UK Patent GB2085461, 1984.

HAPEX™ composites show bioactivity above 0.20 volume fraction hydroxyapatite.

See W. Bonfield, C. Doyle, K.E. Tanner, In Vivo Evaluation Of Hydroxyapatite

Reinforced Polyethylene Composites, Biological and Biomechanical *Performance* of

20   Biomaterials, ed., P. *Christel*, A. *Meunier*, A.J.C. Lee, Elsevier Science Publisher,

1986, pp. 153-158. Additionally, degradable composites of hydroxyapatite and

copolymers of polyhydroxybutyrate and polyhydroxyvalerate have been described.

See C. Doyle, K.E. Tanner, W. Bonfield, In Vitro And In Vivo Evaluation Of

Polyhydroxybutyrate And Of *Polyhydroxybutyrate* Reinforced With Hydroxyapatite,

Biomaterials, Vol. 12, 1991, pp. 841-847. The main limitation of these biostable and

biodegradable composites is their inadequate mechanical strength for large bone

fracture fixation. Also, use of hydroxyapatite and poly lactic acid composites has

been reported. *See* Y. Ikada, H.H. Suong, Y. Shimizu, S. Watanabe, T. Nakamura,

5   M. Suzuki, A.T. Shimamoto, Osteosynthetic Pin, U.S. Patent 4,898,186, 1990.

Using existing elements the composite still has quite moderate mechanical strength.

Also in all these cases mentioned above the method of producing the composite

differs from the method of the present invention.

10   Summary of the Invention

In this invention, we have established that the problems of inadequate strength

and the brittleness of the bioactive bone fixation devices and the lack of bioactivity of

absorbable polymeric devices are resolved by constructing a composite material

comprising at least one resorbable polymeric matrix, at least one bioactive ceramic

15   reinforcing element and at least one resorbable polymeric reinforcing component.

The composite material described in more detail herein consists of two reinforcing

components in a matrix material. One reinforcing element, the polymeric reinforcing

element, is comprised of biodegradable polymer fiber and the other, called the

ceramic reinforcing element, is comprised of bioceramic or bioglass.

20   Reinforced composite devices described in this invention have improved mechanical

properties compared to non-reinforced devices, because reinforcement changes the

behavior of material from brittle to ductile and thus makes device more reliable under

load. Due to controlled manufacturing stages, mixing of matrix and ceramic

reinforcing element as well as combining the polymeric reinforcing element, the

amount of both reinforcing element types is easily controlled. This is an important

advantage, because the ratio of elements affects the mechanical properties of the

device. Also, the amount of the ceramic reinforcing element affects the bioactivity of

the device.

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Brief Description of the Drawings

Figure 1 Shows a schematic picture of the cross-section of a composite plate

of the invention.

Figure 2a Shows a FTIR spectrum of hydroxyapatite,

10   Figure 2b Shows a FTIR spectrum of hydroxyapatite-poly lactic acid

composite, and

Figure 2c Shows a FTIR spectrum of poly lactic acid composite.

Description of the Preferred Embodiments

15   This invention relates to biodegradable materials used for bone fracture

fixation devices and methods of their manufacture. Unlike other known materials

used prior to this application, the composites of this invention have two different

reinforcing phases and one matrix phase. One reinforcing element is referred as the

polymeric reinforcing element and the other as the ceramic reinforcing element. The

20   matrix component can be any biodegradable or bioerodible polymer. Typical

examples of these polymers are listed in Table 1 herein.

One reinforcing phase is a totally or at least partially oriented and/or

fibrillated biodegradable or bioerodible polymer. This phase is called the polymeric

reinforcing element, which is still recognizable and distinguishable from the final

product as a whole. The diameter of the reinforcing fibers can vary between 4 μm and 800 μm, preferably between 20 μm and 500 μm. Useful polymers for the polymeric reinforcing element include those listed in Table 1.

The ceramic reinforcing element can be comprised of a stable or a degradable bioceramic or bioglass, or a mixture of these. Typical examples are listed in Table 2. They can be used in a powder, flake, spherical, fiber or any other form. Particle size can vary between 2 μm and 100 μm, preferably between 60 μm and 150 μm. In the case of fibers, the fibers are in all cases smaller than the polymeric reinforcing elements. The ceramic reinforcing element also acts as a bioactive, bony ongrowth agent and provides a reservoir of calcium and phosphate ions, thus accelerating the healing time for bone fractures. While the matrix polymer degrades, bone can attach to the residual ceramic or glass particles. The amount of ceramic reinforcing element is 0.15 to 0.9 volume fraction, preferably between 0.2 and 0.6 volume fraction.

The defined particle size of the ceramic element in the composite described in this invention is relatively big compared to conventionally used particle sizes for fillers or granules. In this invention, it was found unexpectedly that composites having bigger particle size ceramic elements are more biocompatible and cause less irritation to tissue than composites utilizing a ceramic element having small particle size. Biocompatibility is easily seen in histological studies. In tissue near and inside the degrading composite implants having small ceramic particles there exists more giant cells than around and inside the degrading composite implants containing big (coarser) ceramic particles.

The invention may contain various additives and modifiers which improve the processability of the composite. Such additives include surface modifiers to improve

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the attachment between the polymeric and ceramic components. The devices can also contain pharmaceutically active agent or agents, such as antibiotics, chemotherapeutic agents, wound-healing agents, growth hormones and anticoagulants (such as heparin). These agents are used to enhance the bioactive

5   feature of the composite and thus improve the healing process of the tissue.

Manufacture of the composite can be performed by any suitable plastics technology processing method. The matrix polymer and the ceramic reinforcing element(s) (bioceramic or bioglass) can be mixed together by powder mixing, melt mixing or solvent mixing. The polymeric reinforcing element (polymer fiber) can be

10   used as plain fiber or in modified form: for example, as braided or woven two or three dimensional structures. The mixture of matrix and the ceramic reinforcing element can be combined with the polymeric reinforcing element by melt mixing, by coating or by using solvent as an intermediate to preform the material (prepreg). The material can be produced in its final form by various techniques, including

15   compression molding, filament winding, mechanical machining or injection molding to any desired shape.

Due to controlled manufacturing stages, mixing of matrix and ceramic reinforcing element as well as combining the polymeric reinforcing element, the amount of both reinforcing element types is easily controlled. This is an important

20   advantage, because the ratio of elements affects the mechanical properties of the device. Also, the amount of the ceramic reinforcing element affects the bioactivity of the device. There should be sufficient bioceramic or bioglass to yield bony ongrowth.

Reinforced composite devices described in this invention have improved mechanical properties compared to non-reinforced devices, because reinforcement

changes the behavior of the material from brittle to ductile and thus makes the reinforced device more reliable under load. This feature is very important for load bearing applications, such as bone fracture fixation devices. For example, non-reinforced poly lactic acid devices typically have three-point bending strengths of

5   35-40 MPa and moduli of 3.5-4.0 GPa, and particulate reinforced (hydroxyapatite) poly lactic acid devices have values of 25-30 MPa and 5.0 GPa, respectively. Using polymer fiber reinforcement under the present invention, mechanical properties of two to five times higher are achieved.

10   EXAMPLES

The present invention is described in more detail by means of the following, non-limiting examples.

Example 1.

15   Plates sized approximately 50 x 10 x 2 mm were manufactured by compression molding from a powder mixture of poly (L,D-lactide) (95/5 L/D ratio) and hydroxyapatite with particle size of 60 μm, reinforced unidirectionally with poly (L-lactide) fibers (53/35/12 weight percent of matrix polymer-hydroxyapatite - polymer fiber, respectively). Three-point bending strength (yield) and modulus were

20   69.8 MPa and 5.8 GPa, respectively, and no sample fracture was detected (ductile behavior). These results were compared to the results of similarly sized samples without fiber reinforcement, compression molded from (1) plain PLDLA 95/5 and from (2) powder mixture of PLDLA 95/5 and hydroxyapatite (60/40 w/w %). These samples showed three-point bending strengths (maximum) and moduli of (1): 38.0

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MPa and 3.9 GPa and (2): 26.8 MPa and 5.0 GPa, respectively. These samples broke in bending without yielding, thus showing brittle fracture behavior.

Example 2.

5   Plates sized as in example 1 were manufactured by compression molding from a mixture of poly (L,D-lactide) (85/15 L/D ratio) and hydroxyapatite with particle size of 60 μm reinforced unidirectionally with poly (L-lactide) fibers. Poly (L,D-lactide) and hydroxyapatite were previously melt mixed to a film form. The composition had 48/21/31 weight percent of matrix polymerhydroxyapatite-polymer

10   fibers, respectively. Three-point bending strength (yield) and modulus were 116.6 MPa and 6.1 GPa, respectively, and no sample fracture was detected.

Example 3.

       Plates sized approximately 50 x 10 x 1 mm were manufactured by

15   compression molding from the unidirectional prepreg material of poly (L,D lactide) (85/15 L/D ratio), hydroxyapatite and poly (L-lactide) fibers. The proportions of components varied from 3-16 wt-%, 15-50 wt-% and 48-85 wt-%, respectively. Three-point bending strength (yield) and modulus depended on the concentrations of the composite. Typical mechanical properties are listed in Table 3. No sample

20   fracture was detected and the behavior was ductile.

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Table 3

PLDLA (85/15) matrix (wt-%)	PLLA fibers (wt-%)	Hydroxy apatite (wt-%)	Three-point bending strength (MPa)	Three-point bending modulus (GPa)
3	82	15	136	9.5
4	71	25	143	9.1
5	47	48	141	12.2
8	61	31	139	10.5
9	54	37	118	8.3
16	48	36	166	9.6

Example 4.

Plates sized as in example 3 were manufactured by compression molding from a prepreg material of poly (L,D-lactide) (85/15 L/D ratio), hydroxyapatite and poly (L-lactide) fibers. The proportions of components were 4 wt-%, 15 wt-% and 81 wt-%, respectively. Three sample types were manufactured having different prepreg lay-ups of 0°/0°/0°/0°/0°, 0°/45°/0°/-45°/0° and 0°/0°/90°/0°/0°. Three-point bending strengths (yield) and moduli were 135.9 MPa and 9.5 GPa, 140.1 MPa and 10.1 GPa, and 131.0 MPa and 9.3 GPa, respectively, and no sample fracture was detected.

Example 5.

The surfaces of three different samples were studied by Fourier Transform Infrared Spectroscopy. Samples were:

a) hydroxyapatite

b) hydroxyapatite-poly (D,L-lactide)-poly (L-lactide) composite

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c) poly (D,L-lactide)-poly (L-lactide) composite.

The spectras from these samples are shown in figure 2. Matching peaks are detectable with samples b and c, which are poly lactide peaks. There also occur matching peaks from samples a and b which are characteristic of calcium phosphate compounds. The bioactivity of the composites claimed in this invention is the result of hydroxyapatite on the surface.

Example 6.

Plates sized as in example 3 were manufactured by compression molding from the unidirectional prepreg material of racemic poly (D,L-lactide), tricalcium phosphate with mean particle size of 70 μm and poly glycolide fibers. The proportions of components varied from 5 wt-%, 20 wt-% and 75 wt-%, respectively. Three-point bending strength (yield) and modulus were 195 MPa and 14.2 GPa, and no sample fracture was detected.

Example 7.

Plates sized as in example 3 were manufactured by compression molding from the prepreg material made of racemic poly (D,L-lactide), hydroxyapatite powder with mean particle size of 100 μm and the fabric made of poly (L-lactide) and poly (L,D lactide) (96/4) fibers. The proportions of components varied from 5 wt-%, 20 wt-% and 75 wt-%, respectively. Three-point bending strength (yield) and modulus were 150 MPa and 11.8 GPa, and no sample fracture was detected. Specimens showed similar mechanical properties in both the warp and the weft directions of the fabric.

Example 8.

Plates sized as in example 1 were manufactured by compression molding from

a mixture of poly (ortho ester) and hydroxyapatite with mean particle size of 80 μm

reinforced unidirectionally with poly (ortho ester) fibers. Poly (ortho ester) matrix

5   and hydroxyapatite were previously melt mixed to a film form. The composition had

50/20/30 weight percent of matrix polymerhydroxyapatite-polymer fibers,

respectively. Three-point bending strength (yield) and modulus were 105 MPa and

9.7 GPa, respectively, and no sample fracture was detected.

10   Example 9.

Plates sized as in example 3 were manufactured by compression molding from

the unidirectional prepreg material of copolymer of poly (D,L lactide) and

poly-e-caprolactone, tricalcium phosphate with mean particle size of 80 μm and

poly-e-caprolactone fibers. The proportions of components varied from 16 wt-%, 30

15   wt-% and 54 wt-%, respectively. Three-point bending strength (yield) and modulus

were 86 MPa and 3.4 GPa, and no sample fracture was detected. The strength and

modulus values were lower than those for lactide based composites, but the extension

to yield was much higher.

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Example 10.

Plates sized as in example 1 were manufactured by compression molding from

a mixture of a copolymer of poly (hydroxybutyrate)-poly (hydroxyvalerate) and a

mixture of hydroxyapatite and tricalcium phosphate (50/50) with mean particle size

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of 120 μm, reinforced unidirectionally with poly (hydroxybutyrate) fibers. The polymer matrix and ceramic mixture were previously melt mixed to a film form. The composition had 30/30/40 weight percent of matrix copolymer-ceramic mixture-polymer fibers, respectively. Three-point bending strength (yield) and

5   modulus were 122 MPa and 6.2 GPa, respectively, and no sample fracture was detected.

Example 11.

Two set of samples (plates with 5 mm width, 20 mm length and 0.9 mm

10   thickness) were implanted to the back of rats (subcurris). Specimens were made of poly-L lactic acid fibers, poly-D,L-lactic acid matrix (with L/D ratio 85/15) and hydroxyapatite powder using prepreg manufacturing method. The quantities of the components were 80 wt-%, 5 wt-% and 15 wt-%, respectively. The plates had five prepreg layers, with layer alignments of 0°/0°/0°/0°/0°. The mean particle diameter

15   of hydroxyapatite powder in the first set of plates was 7.43 micrometers and in the second set of plates was 80±20 micrometers.. The plates were gamma sterilized with a dose of 2.5 MRads.

Five animals from both sets were sacrificed after one year of implantation. In histological studies it was clearly seen, that in and around the composite plates with

20   finer hydroxyapatite powder there existed significantly more giant cells than in the tissue of reference animals containing composite plates with coarser hydroxyapatite particles. Thus, coarser hydroxyapatite particles were shown to be more biocompatible.

TABLE 1. Resorbable polymers suitable for biocomposites.

Polymer

Polyglycolide (PGA)

Copolymers of glycolide:

Glycolide/L-lactide copolymers (PGA/PLLA)

Glycolide/trimethylene carbonate copolymers (PGA/TMC)

Polylactides (PLA)

Stereocopolymers of PLA:

Poly-L-lactide (PLLA)

Poly-DL-lactide (PDLLA)

L-lactide/DL-lactide copolymers

Copolymers of PLA:

Lactide/tetramethylglycolide copolymers

Lactide/trimethylene carbonate copolymers

Lactide/d-valerolactone copolymers

Lactide/e-caprolactone copolymers

PLA/polyethylene oxide copolymers

Polydepsipeptides

Unsymmetrically 3,6-substituted poly-1,4-dioxane-2,5-diones

Poly-b-hydroxybutyrate (PHB)

PHB/b-hydroxyvalerate copolymers (PHB/PHV)

Poly-b-hydroxypropionate (PHPA)

Poly-p-dioxanone (PDS)

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Poly-d-valerolactone

Poly-e-caprolactone

Methylmethacrylate-N-vinyl pyrrolidone copolymers

Polyesteramides

Polyesters of oxalic acid

Polydihydropyrans

Polyalkyl-2-cyanocrylates

Polyurethanes (PU)

Polyvinylalcohol (PVA)

Polypeptides

Poly-b-malic acid (PM LA)

Poly-b-alkanoic acids

Polycarbonates

Polyorthoesters

Polyphosphates

Table 2. Bioceramics and glasses suitable for biocomposites.

Hydroxyapatite

Tricalciun phosphate

Other calcium phosphates

Bioglass®

Ceravital®

Alumina

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Zirconia

Bioactive gel-glass

Bioactive glasses

Alpha wollastonite glass ceramic